

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 393 572**  
**A3**

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 90107243.9

(51) Int. Cl.<sup>5</sup>: **A61K 31/445, A61K 9/22**

(22) Date of filing: 17.04.90

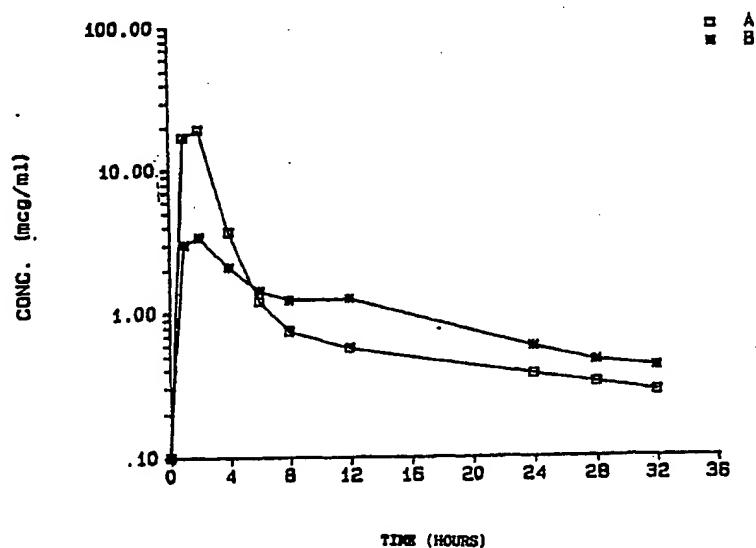
(30) Priority: 20.04.89 IT 2021289

(43) Date of publication of application:  
24.10.90 Bulletin 90/43(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IT LI LU NL SE(88) Date of deferred publication of the search report:  
28.11.90 Bulletin 90/48(71) Applicant: **RECORDATI S.A. CHEMICAL and  
PHARMACEUTICAL COMPANY**  
Corso S. Gottardo 54**CH-6830 Chlasso(CH)**(72) Inventor: **Santus, Giancarlo**  
Via Zuara 8  
I-20146 Milan(IT)  
Inventor: **Tajana, Alberto**  
Via G. Omboni 3  
I-20129 Milan(IT)(74) Representative: **Gervasi, Gemma et al**  
**NOTARBARTOLO & GERVASI** Srl Viale  
Bianca Maria 33  
I-20122 Milan(IT)(54) **Controlled release tablets containing flavoxate.**

(57) Tablets for the controlled release of flavoxate hydrochloride particularly suitable for high active principle doses are described. The characteristic components of these tablets are: a matrix allowing gradual release of the active principle contained

within it, a suitable binder which limits the dimensions of the finished tablet, and an acidifying agent which ensures stability of the active principle with time and improves its release profile by making it independent of the pH.

FIG. 1



EP 0 393 572 A3



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number

EP 90 10 7243

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
D,Y	EP-A-0 250 374 (RECODATI INDUSTRIA CHIMICA E FARMACEUTICA) * Page 3, lines 4-33; pages 11,12, example 10; claims 1,2,6-9,14 * ---	1-8	A 61 K 31/445 A 61 K 9/22
Y	EP-A-0 266 707 (SCHERING CORP.) * Page 2, line 1 - page 5, line 16; claims 1-8 * -----	1-8	
			TECHNICAL FIELDS SEARCHED (Int. Cl.5)
			A 61 K
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 18-09-1990	Examiner BOULOIS D.J-M.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ----- & : member of the same patent family, corresponding document	

(19)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 393 572**  
**A2**

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 90107243.9

(51) Int. Cl.<sup>5</sup>: A61K 31/445, A61K 9/22

(22) Date of filing: 17.04.90

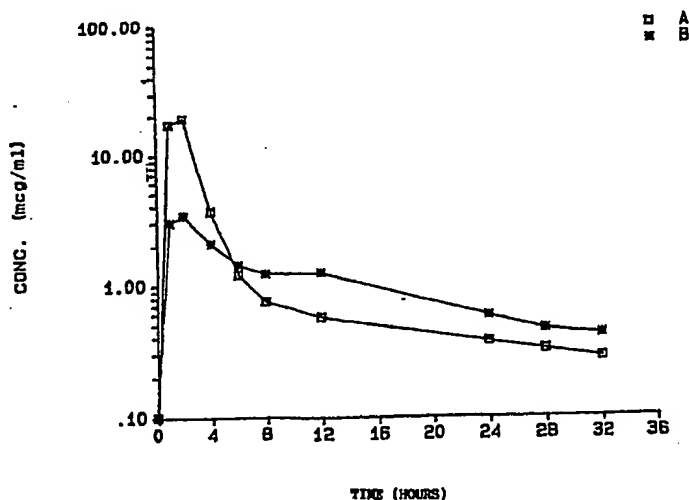
(30) Priority: 20.04.89 IT 2021289

(43) Date of publication of application:  
24.10.90 Bulletin 90/43(84) Designated Contracting States:  
AT BE CH DE DK ES FR GB GR IT LI LU NL SE(71) Applicant: RECORDATI S.A. CHEMICAL and  
PHARMACEUTICAL COMPANY  
Corso S. Gottardo 54  
CH-6830 Chiasso(CH)(72) Inventor: Santus, Giancarlo  
Via Zuara 8  
I-20146 Milan(IT)  
Inventor: Tajana, Alberto  
Via G. Omboni 3  
I-20129 Milan(IT)(74) Representative: Gervasi, Gemma et al  
NOTARBARTOLO & GERVASI Srl Viale  
Bianca Maria 33  
I-20122 Milan(IT)

(54) Controlled release tablets containing flavoxate.

(57) Tablets for the controlled release of flavoxate hydrochloride particularly suitable for high active principle doses are described. The characteristic components of these tablets are: a matrix allowing gradual release of the active principle contained within it, a suitable binder which limits the dimensions of the finished tablet, and an acidifying agent which ensures stability of the active principle with time and improves its release profile by making it independent of the pH.

FIG. 1



EP 0 393 572 A2

## CONTROLLED RELEASE TABLETS CONTAINING FLAVOXATE

This invention relates to a formulation for controlled release tablets containing as active principle 2,N-piperidinoethyl-3-methylflavone-8-carboxylate hydrochloride, otherwise known as flavoxate hydrochloride and indicated as such hereinafter.

Flavoxate hydrochloride is a drug which has long been used in therapy to limit the symptoms of pollakiuria, particularly nocturia, and of urinary incontinence originating from various pathological situations such as prostatitis, urethritis, cystitis and the side effects of radiotherapy or surgical therapy of the urinary tract. It has also been found that flavoxate is effective in the treatment and diagnosis of erectile impotence.

The therapeutic dose is usually 600-800 mg/day in 3-4 administrations, although in some cases a dose of up to 1200 mg/day has been found more effective.

The problem in administering flavoxate hydrochloride derives from the fact that its half life is such that the duration of its therapeutic activity is about 5-6 hours. This period is for example insufficient to provide a patient suffering from nocturia a dose of the drug able to effectively cover his need during the night.

Thus, a formulation able to maintain the therapeutic effectiveness of the drug for a longer time would reduce the frequency of administration, so considerably improving the quality of life of the patient, especially considering that the therapy using flavoxate is prolonged and is particularly directed towards patients of advanced age.

For that reason it should be noted that among all the possible pharmaceutical forms in which flavoxate hydrochloride can be administered, tablets or pills are the most suitable because they ensure that the exact prescribed quantity of product is taken. In addition, for practical reasons, it is advantageous for the administration to take the form of just one item the smallest possible number of times per day.

As far as it is known to the applicant, up to the present time only Japanese patent application JP 63-154619 and European patent application EP 250374 have confronted the problem of administering flavoxate hydrochloride by delayed-release formulations. However, even by applying the teachings of these two patent applications, it is not possible to prepare pharmaceutical forms which allow a single administration when dosages of the active principle are very high. In fact, in such cases, the final product would be of a size practically unacceptable to use.

There is therefore a consequent requirement for formulations comprising a high active principle dosage which provide the total requirement, but are of limited size.

According to the present invention such a formulation, having the desired characteristics and also an acceptable finished product size, can be obtained by including the active principle in a suitable polymer or mixture of polymers to form the controlled-release system, and adding to this system a suitable binder, the essential purpose of which is to maintain the dimensions of the finished product within predetermined limits.

The basic characteristic of this formulation is the presence of the active principle in mixture with polyvinylalcohol (PVA) and a hydrophilic polymer derived from cellulose such as hydroxy propylmethyl cellulose (HPMC), in accordance with the known technique of hydrophilic matrices swellable in an aqueous environment.

In this respect it should be noted that the active principle Flavoxate hydrochloride is in itself hardly compressible so that the use of traditional binders such as gelatine, starch- water or the like would imply an excipient / active principle ratio such that the finished product would certainly exceed a commercially acceptable overall size. The use of PVA makes large-scale use of excipients superfluous, thus enabling the tablet dimensions to be limited.

Furthermore a characteristic of this formulation is that, because of the materials used, the dissolution profile of flavoxate hydrochloride is not affected by the compression strength. This can be considered a remarkable advantage because this makes easier and safer the manufacturing procedure.

It should also be noted that in its unsalified form, flavoxate is not very soluble, so that it would be advantageous to keep it salified while being in the intestinal environment, where there is a tendency for its gradual desalification due to the basic pH, and moreover it is known (Arzneim. Forsch. 25, 1707 (1975)) that in a pH 7.4 phosphate buffer the product half life is about one hour.

The present invention also obviates the aforesaid drawbacks inherent in flavoxate hydrochloride.

In this respect, it has been found that by introducing into the tablet composition a suitable substance of acid character in appropriate quantities, an acid microenvironment is created about and within the pharmaceutical form.

In addition to favouring stability of the active principle this microenvironment maintains optimum conditions for the external diffusion of the active principle even when the external environment has the inherent basic conditions of the intestinal tract.

Substances particularly suitable for the said purpose have been found to be tartaric acid or, alternatively, citric acid.

Specifically, the present invention consists of tablets for the controlled release of flavoxate hydrochloride composed of:

- 5 a) Flavoxate hydrochloride as active principle.
- b) A polymer or mixture of polymers which structure the matrix allowing gradual release of the active principle contained in it. The polymer or polymers which can be used for this purpose are generally any type of natural or synthetic polymer able to swell on contact with water, such as: methylcellulose of various molecular weights, polyvinylalcohols, acrylic copolymers and hydroxypropyl methylcellulose (HPMC). It is  
10 generally possible to operate with a polymer quantity within 5 and 10% by weight of the total weight of the finished compound. HPMC (Methocel K15M) is particularly preferred, in a 1:10 w/w ratio to the active principle.
- c) A suitable binding agent such as polyvinylpyrrolidone (PVP), cellulose or PVA, generally in a quantity of between 1% and 5% of the total weight. PVA is preferably used in a 1:20 w/w ratio to the active  
15 principle, this ensuring the formation of a tablet of acceptable technological dimensions such as to favour the compliance of the patient.
- d) A suitable acidifying agent for maintaining the solubility of the active principle even in a basic environment while at the same time favouring its stability. Suitable substances include tartaric acid, citric acid, phosphates and the like. Tartaric acid or citric acid is preferred in a 1:8 w/w ratio to the active  
20 principle.
- e) A suitable lubricant system to enable the tablets to be produced on high-speed presses. The lubricant can be a common lubricant known in the art. A talc / magnesium stearate mixture is preferred in freely variable proportions, provided that the total weight of the mixture is within 1-3% by weight of the finished product.
- 25 f) Optionally, to improve the palatability of the tablet given the bitter taste of flavoxate hydrochloride, the tablet can be coated, following known methods, with suitable substances. These substances, which must in any event be readily soluble and such as not to influence the release characteristics, can be chosen either from aqueous coatings or non-aqueous coatings.

The tablets of the present invention can be produced by common presses in accordance with the  
30 known art as described in greater detail in the following examples.

Stability data at room temperature confirm a good stability of flavoxate hydrochloride with unchanged dissolution patterns of the tablets.

In these examples reference is also made to the results obtained on using the tablets, the purpose of these examples being to better illustrate the invention and to show its advantages and applicability, but  
35 without in any way constituting a limitation thereon.

#### EXAMPLE 1

40 The standard percentage composition and preparation method are described for controlled release tablets containing 400, 600 and 800 mg of flavoxate HCl as active principle.

Composition	%
45 Flavoxate HCl	76.9
Hydroxypropylmethylcellulose (Methocel K15M)	7.7
Polyvinyl alcohol	3.8
Magnesium stearate	0.8
Tartaric acid	9.6
50 Talc	1.2

#### 55 Preparation method

The flavoxate HCl and hydroxypropylmethylcellulose are mixed together and then made into a paste with the aqueous polyvinyl alcohol solution. The paste is granulated and dried to a water content of less

than 3% and is then mixed with tartaric acid, talc and magnesium stearate. The mixture is then compressed with a rotary press fitted with suitable punches. Alternatively the tartaric acid can be added at the beginning, directly into the paste to be granulated.

## EXAMPLE 2

To improve their palatability the tablets obtained by the method described in Example 1 can be coated by known methods with a solution having the following composition:

Composition	%
Methocel E 5	5.7
Talc	7.4
Titanium dioxide	5.0
Saccharose	1.1
Polyethyleneglycol 6000	1.1
Water	79.6

### Coating procedure

The coating solution, which provides a completely water-soluble coating, is sprayed in a pan onto the tablets preheated to 45°C. During the process the temperature is maintained at a level suitable to ensure good water evaporation.

To demonstrate the characteristic of the above formulation, data are provided regarding in vitro tablet dissolution tests.

These data emphasize the independence of the formulation from the pH of the medium, its stability and the independence from the compression strength.

An in vivo study on the hematic levels prevailing after taking the tablets is also provided.

## EXAMPLE 3

### Dissolution

The cumulative dissolution of the tablets was investigated in vitro using the apparatus II of U.S. Pharmacopoeia XXI Ed., using as dissolution medium a) 900 ml of 0.1 N HCl and b) 900 ml of pH 7.4 phosphate buffer respectively. The temperature was maintained at 37°C and the rotational speed of the paddle at 60 rpm. Samples were withdrawn every hour and the percentage dissolution was determined by U.V. spectrophotometry, reading the absorbance at 291 nm.

Tables 1 and 2 show the experimental results expressed as cumulative % of substance dissolved per unit of time under various conditions, related to the quantity of substance initially present.

The dissolution of tablets respectively containing 400 mg (A) and 600 mg (B) of active principle and furthermore both containing tartaric acid in their formulation, is compared with the dissolution of tablets containing 400 mg (C) of active principle having no acidifying agent in their formulation.

As can be seen, the presence of the acidifying agent in the tablets renders the dissolution independent from the pH of the dissolving medium and in particular improves the dissolution of the active principle at pH 7.4 (Table 2, formulations A or B vs. C).

TABLE 1

Cumulative dissolution in 900 ml 0.1 N HCl			
Time hours	A	B	C
	% (q s.d.)	% (q s.d.)	% (q s.d.)
1	3.95 (0.42)	5.55 (0.26)	5.03 (0.22)
2	8.22 (1.01)	9.69 (0.54)	6.61 (0.36)
3	13.21 (1.58)	15.50 (0.91)	11.89 (0.52)
4	18.20 (2.12)	20.50 (0.94)	15.98 (0.82)
5	22.94 (2.57)	26.11 (1.25)	20.32 (1.13)
6	27.68 (3.06)	31.63 (1.64)	24.70 (1.00)
7	32.42 (3.60)	36.60 (1.54)	29.80 (1.58)
8	38.63 (4.13)	42.03 (1.28)	33.13 (1.76)

TABLE 2

Cumulative dissolution in 900 ml phosphate buffer pH 7.4			
Time hours	A	B	C
	% (q s.d.)	% (q s.d.)	% (q s.d.)
1	6.15 (0.36)	8.28 (0.59)	1.12 (0.19)
2	14.24 (1.08)	18.43 (0.55)	1.39 (0.23)
3	19.73 (1.47)	26.58 (0.61)	2.25 (0.24)
4	28.52 (2.17)	34.08 (0.58)	2.38 (0.28)
5	32.20 (2.71)	39.74 (1.80)	2.72 (0.26)
6	41.02 (1.85)	48.25 (1.97)	3.19 (0.36)
7	44.67 (2.64)	51.46 (2.25)	3.66 (0.31)
8	48.15 (2.82)	53.31 (4.35)	3.84 (0.37)

## EXAMPLE 4

45 Influence of compression strenght on dissolution

Tablets having the composition described in Example 1 were compressed using an instrumented rotary press at the three different compression strengths of: 5 kN (D), 10 kN (E), 16 kN (F).



TABLE 3

Cumulative dissolution in 900 ml 0.1 N HCl			
Time hours	D (5 kN)	E (10 kN)	F (16 kN)
	% ( $\pm$ s.d.)	% ( $\pm$ s.d.)	% ( $\pm$ s.d.)
1	8.61 (1.10)	8.01 (1.17)	7.97 (0.88)
2	13.97 (0.95)	15.43 (1.32)	13.46 (1.98)
3	18.29 (1.47)	19.88 (1.15)	19.21 (1.58)
4	22.66 (1.46)	24.34 (1.40)	25.15 (2.91)
5	28.83 (1.41)	31.87 (1.51)	30.69 (1.87)
6	34.93 (1.68)	39.45 (2.97)	36.24 (4.09)
7	39.49 (0.98)	44.94 (1.89)	41.25 (3.59)
8	44.04 (1.87)	50.42 (3.71)	46.26 (4.14)

As can be seen, the compression strength does not affect the dissolution profile of flavoxate hydrochloride from this formulation.

#### EXAMPLE 5

##### Stability

The dissolution of Tablets having the composition described in Example 1 and containing 600 mg of active principle, was investigated after 1 year storage at room temperature (15-25°C).

The corresponding data are reported in table 4 (solution of 0.1 N HCl) and table 5 (solution of phosphate buffer pH 7.4) respectively.

TABLE 4

Cumulative dissolution in 900 ml 0.1 N HCl		
Time hours	initial	1 year
	% ( $\pm$ s.d.)	% ( $\pm$ s.d.)
1	5.55 (0.26)	4.55 (0.25)
2	9.69 (0.54)	8.28 (0.87)
3	15.50 (0.91)	13.52 (1.52)
4	20.50 (0.94)	18.84 (2.14)
5	26.11 (1.25)	24.29 (2.77)
6	31.63 (1.64)	29.41 (2.26)
7	36.60 (1.54)	34.86 (2.69)
8	42.03 (1.28)	39.82 (2.69)

TABLE 5

Cumulative dissolution in 900 ml phosphate buffer pH 7.4		
Time hours	initial	1 year
	% ( $\pm$ s.d.)	% ( $\pm$ s.d.)
1	8.28 (0.59)	6.23 (0.43)
2	18.43 (0.55)	16.89 (0.82)
3	26.58 (0.61)	24.78 (1.01)
4	34.08 (0.58)	31.98 (1.23)
5	39.74 (1.80)	38.14 (2.05)
6	48.25 (1.97)	46.54 (2.15)
7	51.46 (2.25)	49.98 (2.56)
8	53.31 (4.35)	52.04 (2.84)

As can be seen, in both cases there is no difference between initial and 1 year data at two different pH values.

#### EXAMPLE 6

##### Hematic levels

A cross-over trial was carried out in two periods using a single dose. The trial was conducted on 6 healthy volunteers who had received a 400 mg controlled release tablet of flavoxate hydrochloride formulated as described in Examples 1 and 2, or as reference, two 200 mg flavoxate hydrochloride tablets in the currently commercially available formulation (Genurin SF<sup>R</sup>). The plasmatic concentration of the principal metabolite of flavoxate, namely 3-methylflavone-8-carboxylic acid (MFCA), was then measured.

Figure 1 shows the mean MFCA plasmatic levels attained in the trial. The vertical axis represents concentration in mcg/ml and the horizontal axis represents time in hours. The curve indicated by A represents the levels attained after administering Genurin SF, while the curve indicated by B represents the levels attained after administering the controlled release formulation.

From Figure 1 it can be seen that when the active principle is administered by means of the tablets formulated in accordance with the present invention, the time for which therapeutically effective levels are available is much longer (mean value 11.35 hours for curve B and 6.74 hours for curve A at plasmatic concentrations greater than or equal to 1 mcg/ml, this being the minimum effective value).

##### Claims

1. Tablets for the controlled release of therapeutically effective quantities of flavoxate hydrochloride, their composition being characterised by the presence, together with the active principle and a suitable lubricant, of:

- a polymer or a polymer mixture forming the controlled release matrix;
- a binding agent used in a minimum quantity with respect to the active principle, such as to allow the formulation of tablets of acceptable dimensions even for large doses;
- an acidifying agent able to create, about and within the tablet, an acid microenvironment able to ensure the stability of the active principle and to improve its release profile by making it independent of the pH.

2. Tablets as claimed in claim 1, wherein the polymer mixture in a) consists of hydroxypropylmethylcellulose, preferably in a ratio of 1:10 w/w to the active principle.

3. Tablets as claimed in the preceding claims, wherein the binding agent in b) is polyvinyl alcohol (PVA), preferably in a ratio of 1:20 w/w to the active principle.

4. Tablets as claimed in the preceding claims, characterized in that the dissolution profile of the active principle is not affected by the strength applied during the compression phase.

5. Tablets as claimed in the preceding claims, wherein the acidifying agent in c) is citric acid or tartaric acid, preferably in a ratio of 1:8 w/w to the active principle.

5 6. Tablets as claimed in the preceding claims, characterized in that the content of the active principle and its dissolution profile do not change with time.

7. Tablets as claimed in the preceding claims, covered with a water-soluble film.

8. Tablets as claimed in the preceding claims, containing from 400 mg to 1200 mg of flavoxate hydrochloride as active principle.

10

15

20

25

30

35

40

45

50

55

FIG. 1

